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Understanding the Pathophysiology and Management of the Anxiety Disorders

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ABSTRACT

Anxiety is a general psychiatric state characterized by fear, worry, unnecessary violent behavior, poor quality of life, avoidance and the compulsive rituals that are related with the significant suffering. Current epidemiological studies of the anxiety disorders provided facts of their elevated incidences in the general population worldwide. Anxiety disorders are extremely widespread in adults especially females show higher preponderance of 2:1 over the males. Anxiety disorders can be measured as "intact" situation, which completely upsets everyday life of the individual. It creates a state of mysterious anticipatory fear and apprehension concerning the incidence of even usual things in life. Drug treatment for the anxiety disorders includes use of latest pharmacological agents acting at definite neurotransmitters and neuropeptides, their reuptake and metabolism. Anxiety disorders are frequent psychiatric conditions that result in poor quality of life, significant disability, and influences enormous social cost. Even though treatments with confirmable efficiency are existing, a large number of patients fail to respond or remain with clinically significant residual symptoms even after management. The treatment resistance involved in anxiety disorders remains a challenge to the clinical practice going from non uniform concepts of response and the resistance to a paucity of controlled studies relating to remedial strategies. This clinical review focuses on the pathophysiologic basis for anxiety disorders, brief overviews of different anxiety disorders, clinical features, diagnosis and the management options for the patients suffering.

INTRODUCTION

Anxiety disorders are among the most prevalent categories of mental illnesses[1,2]. Anxiety disorders are characterized by excessive and unrealistic worry about everyday tasks or events, or may be specific to certain objects or rituals. Recent epidemiological studies of anxiety disorders provided evidence of their high frequency in the general population worldwide. Anxiety disorders afflict an estimated 15.7 million people in the United States each year[3]. Anxiety disorders are highly prevalent in adults especially females show higher preponderance of 2:1 as compared to males[4]. Anxiety is associated with substantial negative effects on children's social, emotional and academic success[5]. When left untreated, anxiety symptoms persist and are associated with significant impairments in functioning, poor quality of life, and a huge economic burden. Anxiety disorders are of particular importance in the context of recent and ongoing world conflicts, as environmental factors can have a strong impact on anxiety disorder development[6]. Although anxiety disorders have been extensively studied, the literature examining underlying neural mechanisms remains scarce, with relatively little evidence identifying specific deficits for various anxiety disorders. Despite the lack of concrete knowledge regarding the specific mechanisms underlying anxiety, both pharmacologic and psychotherapeutic treatments for anxiety management have been developed. These treatments are effective for many patients suffering from anxiety, but the exact mechanisms of action are not well known. Moreover, many patients do not have access to or do not experience complete symptom relief with the existing evidence-based treatments. Alternatively, anxiety is often defined by a more prolonged state of tension, worry, and apprehension regarding uncertain, and potentially negative, future events[7]. Perhaps it is not surprising that nearly one in four of us will experience a clinical level of anxiety within our lifetimes[8]. Anxiety crucially involves uncertainty as to the expectancy of threat, is triggered by less explicit or more generalized causes, and is characterized by a more diffuse state of distress, with symptoms of hyperarousal and worry[9]. It has been suggested that these cognitive biases are implicated in the maintenance, and possibly even the etiology, of anxiety[8].

Anxiety disorders are among the most common mental, emotional, and behavioral problems[1,10,11].These affect one-eighth of the total population worldwide[12,13]. In addition to the high prevalence, anxiety disorders account for major expenditure for their management and

anxiety disorders have a substantial negative impact on quality of life[10]. Drug development in this direction also aims to generate new pharmacological agents with action at specific neurotransmitters and neuropeptides, their reuptake and metabolism. This search has led to development of unconventional agents[14]. The neurobiological approach to delineate the pathophysiology of anxiety also come across the fact anxiety disorders are highly co-morbid with each other and respond to the single or same spectrum of treatments. Different types of anxiety disorders are characterized by the presence of chronic anxiety symptoms that are clinically significant and are part of most prevalent group of psychiatric disorders[1,15]. Patients with anxiety disorders exhibit a significant reduction in their quality of life, less productivity, higher morbidity and mortality, and higher rates of comorbidity[16,17]. Although there are several therapeutic strategies available for the treatment of anxiety disorders, the management of patients who do not respond adequately to the treatment remains a challenge in the clinical practice[15]. Anxiety disorders are responsible for a significant social cost due to individual suffering, as well as indirect social costs[15]. There is huge impact on the health system not only because of the expenses with the treatment, but also because of the more frequent search for medical care caused by anxiety[16,17,18].

SYMPTOMS OF ANXIETY DISORDER

Subjective incident of anxiety characteristically has two components the physical and the emotional which influence the cognitive processes of the person[19,20,21,22,23]. These features have been summarized in the Figure- 1.The clinical sign and symptoms differ depending on the form of anxiety disorder, but general sign and symptoms include the heart palpitations, feelings of panic, fear, and uneasiness, insommnia, cold or sweaty hands and/or feet, shortness of breath, an incapability to be steady and calm, dry mouth, numbness or tingling in the hands or feet, nausea, muscle tension and dizziness[21,22,23].

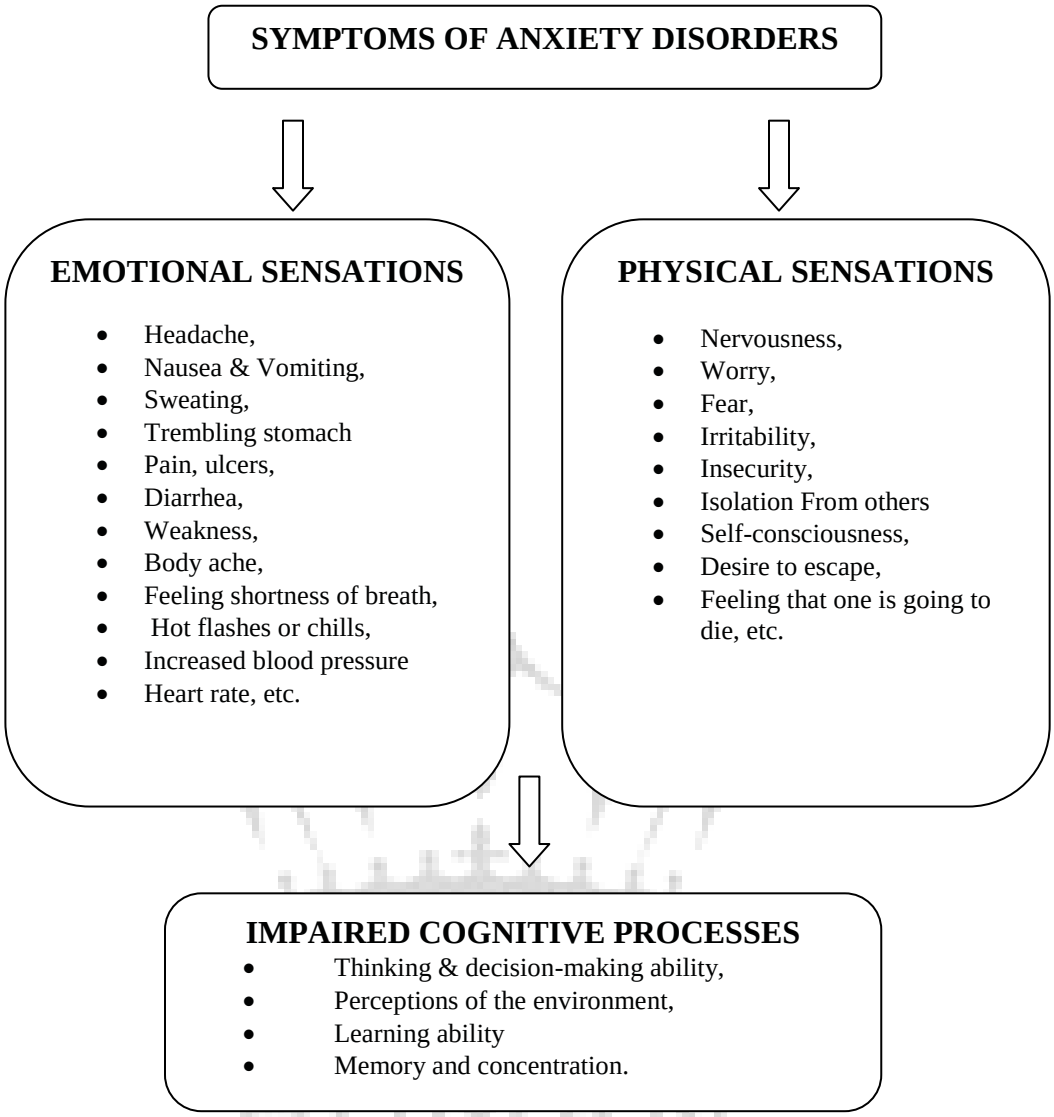

Figure 1: Clinical symptoms of Anxiety Disorders

CAUSES OF ANXIETY DISORDERS

About 500 million people, worldwide, suffer from mental and behavioral disorders [24]. Anxiety disorders, like depression, are among the most prevalent psychiatric disorders. Most anxiety disorders first appear during childhood and adolescence. Evidence shows that a high proportion of children 'do not grow' out of their anxiety disorders during adolescence and adulthood[25]. Different surveys suggest that anxiety affects one-eighth of the total population of the world. The overall lifetime prevalence rate for anxiety disorders is 24.9%. This data suggests anxiety disorders are more chronic than affective or substance abuse disorders[26]. Prevalence of anxiety

disorders is difficult to pinpoint since even small changes in diagnostic criteria, interview tools, or study methodology affect results[26]. Anxiety disorders are among the most frequent mental disorders encountered in clinical practice[27]. As scientists continue their research on mental illness, it is becoming clear that many of these disorders are caused by a combination of factors, including changes in the brain and environmental stress. Like other brain illnesses, anxiety disorders may be caused by problems in the functioning of brain circuits that regulate fear and other emotions. Studies have shown that severe or long-lasting stress can change the way nerve cells within these circuits transmit information from one region of the brain to another. Other studies have shown that people with certain anxiety disorders have changes in certain brain structures that control memories linked with strong emotions. In addition, studies have shown that anxiety disorders run in families, which means that they can at least partly be inherited from one or both parents, like the risk for heart disease or cancer. Moreover, certain environmental factors -- such as a trauma may trigger an anxiety disorder in people who have an inherited susceptibility to developing the disorder[26]. Anxiety disorders represent a heterogeneous group of disorders, probably with no single unifying etiology. Various psychodynamic, psychoanalytic, behavioral, cognitive, genetic and biological theories have been proposed to explain the etiology and pathophysiology of anxiety disorders [26].

Biological factors

Genetic factors predispose certain people to anxiety disorders. There is a higher chance of an anxiety disorder in the parents, children and siblings of a person with an anxiety disorder than in the relatives of someone without an anxiety disorder[27,28].

Neurotransmitter imbalance

Brain imaging and functional studies have shown that several neurotransmitters are linked to the neurobiology of anxiety[29,30,21].

Physiological factors

Anxiety can result when a combination of increased internal and external stresses overwhelm one's normal coping abilities or when one's ability to cope normally is lessened for some reason. The psychological factors are summarized as below:

Psychodynamic: When internal competing mental processes, instincts and impulses conflict, causing distress.

Behavioral: Anxiety is a maladaptive learned response to specific past experiences and situations that become generalized to future similar situations.

Spiritual: When people experience a profound, unquenchable emptiness and nothingness to their lives, often leading to distress concerning their mortality and eventual death[31,32].

Social factors

Life experiences like death in the family, divorce, job loss, financial loss, accident or major illness affect a person's attitude and response to life situations. Long term exposure to abuse, violence, terrorism and poverty may affect an individual's susceptibility to anxiety disorders[33].

Co-existing psychological symptoms and co-morbid mental disorders

Anxiety symptoms often co-exist with other psychological symptoms, especially depressive symptoms, which are particularly frequent among those individuals with more severe anxiety symptoms. High levels of co-morbidity are seen between the anxiety disorders, and with major depression, bipolar disorder, schizophrenia substance misuse and physical illness[34]. The presence of a comorbid anxiety disorder is associated with both a longer time to recovery and with a greater risk of ending treatment prematurely in patients with major depression[34].

DIAGNOSIS OF ANXIETY DISORDERS

Anxiety disorders are a group of mental disorders characterized by various combinations of key features—excessive anxiety, fear, worry, avoidance, and compulsive rituals—that are associated with impaired functioning or significant distress. Anxiety as a feeling state, expressed as physical, emotional, and behavioural responses to perceived threats, is a normal part of everyday life. Certain criteria can help to identify when anxiety becomes a problem and warrants a diagnosis of a disorder (Table 2.1). Some patients may present with complaints of anxiety and stress, drawing attention to the problem immediately. Others will present with sleeplessness, vague pains, headache, dizziness, stomach upset, or other somatic symptoms. Complaints of loss of concentration, tiredness, and reduced effectiveness in routine tasks may also be prominent

symptoms. When a patient presents with excessive or uncontrollable anxiety as described in Table 2.1, it is important to identify other potential causes of the symptoms, including a medical condition, depression, substance use disorder, symptoms secondary to medication, somatoform disorders, or psychotic disorders. However, the presence of these conditions does not preclude the diagnosis of an anxiety disorder, since patients with anxiety disorders frequently have comorbid conditions (see below) and anxiety disorders are more common in patients with certain medical and psychiatric conditions[35].

Anxiety symptoms are common in general population and in primary and secondary medical care. Symptoms may be mild, transient and without associated impairment in social and occupational function, but many patients are troubled by severe and persistent symptoms that cause significant personal distress, impair function and reduce quality of life. To meet the diagnosis of an anxiety disorder, patients have to experience a certain number of symptoms for more than a minimum specified period, the symptoms causing significant personal distress, with an associated impairment in everyday function. Most research in the field has been based on the diagnostic categories for anxiety disorders in the fourth edition of the *Diagnostic and Statistical Manual* (DSM-IV) [IV] [35] which are broadly similar to those in the tenth edition of the *International Classification of Diseases* (ICD-10) [IV] [36]. The DSM system has recently been revised, and it is uncertain whether the approach to anxiety disorders within 'ICD-11' will differ substantially from ICD-10 or DSM-5[36,35].

Table 1: Types of Anxiety Disorders and their clinical symptoms[37].

Types of Anxiety Disorders	Clinical features of anxiety
Panic disorder	''It is characterized by sudden attacks of terror, usually accompanied by a pounding heart, sweatiness, weakness, faintness, or dizziness. During these attacks, people with panic disorder may flush or feel chilled; their hands may tingle or feel numb; and they may experience nausea, chest pain, or smothering sensations. Panic attacks usually produce a sense of unreality, a fear of impending doom, or a fear of losing control.''
OCD	''People with obsessive-compulsive disorder (OCD) have persistent, upsetting thoughts (obsessions) and use rituals (compulsions) to control the anxiety these thoughts produce. Most of the time, the rituals end up controlling them.''

PTSD	‘’Post-traumatic stress disorder (PTSD) develops after a terrifying ordeal that involved physical harm or the threat of physical harm.’’...‘’People with PTSD may startle easily, become emotionally numb (especially in relation to people with whom they used to be close), lose interest in things they used to enjoy, have trouble feeling affectionate, be irritable, become more aggressive, or even become violent.’’
	Specific phobia ‘’A specific phobia is an intense, irrational fear of something that poses little or no actual danger. Some of the more common specific phobias are centered around closed-in places, heights, escalators, tunnels, highway driving, water, flying, dogs, and injuries involving blood. Such phobias aren’t just extreme fear; they are irrational fear of a particular thing.’’
Social phobia	‘’Social phobia, also called social anxiety disorder, is diagnosed when people become overwhelmingly anxious and excessively self-conscious in everyday social situations. People with social phobia have an intense, persistent, and chronic fear of being watched and judged by others and of doing things that will embarrass them. They can worry for days or weeks before a dreaded situation.’’
GAD	‘’People with generalized anxiety disorder (GAD) go through the day filled with exaggerated worry and tension, even though there is little or nothing to provoke it.’’ ... ‘’People with GAD can’t seem to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation warrants.’’

Abbreviations: OCD; obsessive compulsive disorder, PTSD; post-traumatic stress disorder, GAD; generalized anxiety disorder.

Certain risk factors and sociodemographic variables have been associated with anxiety disorders and should increase the clinician’s index of suspicion. The most important factors are family history of anxiety and personal history of stressful or traumatic life events. Each of the anxiety disorders has been shown to run in families, suggesting a genetically mediated component. Anxiety disorders frequently co-occur with other psychiatric disorders (see below); anxiety disorders should be considered in patients being treated for other psychiatric disorders, particularly depression and substance use disorders. Comorbid anxiety disorders can negatively affect the treatment outcome of the other target disorders. There are certain medical conditions, as shown in table-2, the symptoms of which resemble the symptoms of anxiety disorders (e.g., palpitations, tachycardia, chest pain or tightness, shortness of breath, hyperventilation) and, thus, make it difficult to identify anxiety disorders[27,21].

Table 2. Some Medical Diseases with Anxiety-Like Symptoms

Cardiovascular	Angina, arrhythmias, congestive heart failure, myocardial infarction, supraventricular tachycardia, mitral valve prolapse
Endocrine and Metabolic	Hyperthyroidism, hypoglycemia, Addison's disease, Cushing's disease, pheochromocytoma, electrolyte abnormalities, hyperkalemia
Endocrine and Metabolic	CNS tumors, dementia, migraine, pain, Parkinson's disease, seizures, stroke, multiple sclerosis, vertigo
Respiratory system	Asthma, pulmonary edema, embolus, pneumonia, chronic obstructive lung disease
Gastrointestinal	Crohn's disease, ulcerative colitis, irritable bowel syndrome
Others	HIV, systemic lupus erythematosus, anemias

Most psychiatric patients will have two or more concurrent psychiatric diseases (co-morbidity) within their lifetime. Anxiety may be a concomitant symptom of several major psychiatric diseases. Anxiety symptoms are extremely common in patients with mood disorders, schizophrenia, delirium, dementia, and substance use disorders[38].

There are different classes of drugs that cause anxiety like symptoms[26,38,21], and have been tabulated in table-3.

Table 3. Different Classes of Drugs That Cause Anxiety Like Symptoms

CNS stimulants	Amphetamines, caffeine, cocaine, ephedrine, methylphenidate
CNS depressant withdrawal	Alcohol, anxiolytics, barbiturates, narcotic agonists, sedative, hypnotics
Cardiovascular drugs	Captopril, enalapril, digoxin, reserpine, hydralazine
Others	Anticholinergics, anticonvulsants, antihistamines, NSAIDS, antidepressants, antipsychotics, bronchodilators, steroids and thyroid preparations

PATHOPHYSIOLOGY OF ANXIETY DISORDERS

Neurochemicals such as Serotonin, GABA, Dopamine, Neuroepinephrin, and many others have also recently been linked to anxiety disorders. Each chemical plays a very different, but equally important, role in anxiety regulation[38,39,40]. Three major neurotransmitters are involved in anxiety: serotonin, norepinephrine and gamma-aminobutyric acid. Serotonin plays a role in the regulation of mood, aggression, impulses, sleep, appetite, body temperature and pain. A number of medications used to treat anxiety disorders raise the level of serotonin available to transmit messages. Norepinephrine is involved in the fight or flight response and in the regulation of sleep, mood and blood pressure. Acute stress increases the release of norepinephrine. In people with anxiety disorders, especially those with panic disorder, the system controlling the release of norepinephrine appears to be poorly regulated. Some medications help to stabilize the amount of norepinephrine available to transmit messages. GABA plays a role in helping to induce relaxation and sleep, and in preventing overexcitation. Medications known as *benzodiazepines* enhance the activity of GABA, producing a calming effect[41].

Dysfunctions of various neurotransmitters and receptors in the brain have been implicated in anxiety disorders. The 3 neurotransmitters primarily implicated in anxiety are GABA, serotonin (5-HT) and noradrenaline[39,40,41]. Dysregulations in the noradrenergic systems are hypothesized to occur in anxiety disorders. Noradrenaline modulates autonomic arousal mechanisms, including increased heart rate and respiration. This leads to a physiological cascade resulting in panic symptoms such as paraesthesia, numbness and tightness in the chest. GAD is associated with noradrenergic overactivity, serotonin receptor (5-HT1A, 5-HT2C) dysregulation and a decrease in the number of benzodiazepine sites on the GABAA - benzodiazepine receptor complex[41].

Gamma Aminobutyric Acid (GABA)

GABA is the main inhibitory neurotransmitter in the CNS. There are 2 subtypes of GABA receptors GABAA and GABAB. Benzodiazepines bind to the benzodiazepine receptor complex located on the postsynaptic neuron. Such binding augments the effect of GABA leading to the opening of chloride ion channels, causing influx of the chloride ions into the cell resulting in neuronal membrane stabilization[40]. GABA may also influence anxiety levels by mediating the

release of other neurotransmitters such as cholecystokinin and suppressing neuronal activity in the serotonergic and noradrenergic systems. Although it is likely that differing pathophysiologies underlie various anxiety disorders, it is widely believed that the gamma -aminobutyric- acid (GABA) circuits are one of the systems integrally involved in anxiety disorders[42]. Neuroimaging studies have reported reductions in GABA levels and GABAA-benzodiazepine receptor binding in patients with anxiety disorders[40;42]. The Glutamate is the main excitatory central nervous system neurotransmitter and is the counterpart of GABA in this respect[42]. GABA-benzodiazepine receptors are widely distributed in the brain and spinal cord. They are particularly concentrated in portions of the brain thought to be involved in anxiety, including the medial PFC, amygdala, and hippocampus, and results from several studies have indicated abnormalities in this system in patients with anxiety disorders[40].

Serotonin

The 5-HT system is significant for its established role in the treatment of anxiety disorders[42]. Serotonergic pathways arising from the raphé nuclei in the brainstem innervate a wide range of structures thought to be involved in anxiety, including the frontal cortex, amygdala, hypothalamus, and hippocampus[42,43,44]. In addition, serotonergic mechanisms are believed to underlie the biologic activity of a wide range of medications used to treat mood disorders, including its anxiety symptoms. Any of a large number of abnormalities in the serotonergic system, including hypo- or hyper-innervations of key brain structures and/or cellular mechanisms resulting in aberrant neurotransmission may be involved in the etiology of anxiety disorders[40]. Cellular pathology that may contribute to the development of anxiety disorders includes abnormal regulation of 5-HT release and/or reuptake or abnormal responsiveness to 5-HT signaling. The 5-HT1A receptor is thought to play a particularly important role in anxiety. Activation of 5-HT1A receptors enhances potassium currents and inhibits the activity of adenylate cyclise[45]. These receptors are localized as inhibitory autoreceptors on the dendrites of serotonergic cell bodies in the raphé nuclei and are also present on non–5-HT neurons in the hippocampus, entorhinal cortex, septum, amygdala, periaqueductal gray and frontal cortex. Long-term stress desensitizes presynaptic 5-HT1A receptors, an action that potentiates serotonergic neurotransmission. Activation of 5-HT1A receptors is also involved in the induction of adrenocortical trophic hormone and corticosteroid secretion in response to stress[41]. The 5-

HT1A receptor is also involved in panic disorder. A specific polymorphism in the gene encoding the 5-HT1A receptor has been shown to have significant associations with both agoraphobia and panic disorder. Serotonergic neurons are implicated in the alteration of appetite, energy, sleep, mood and cognitive function in anxiety. Its role in anxiety is supported by its modulating effect on the locus ceruleus and its projections to the amygdale; anatomical structure almost conclusively implicated in anxiety. Fear and stress activate serotonergic pathways[46,47].

The central and peripheral norepinephrine system, because of its role in the adaptive response to acute physiologic and psychologic stressors, has been a natural focus of investigation concerning the pathophysiology of anxiety disorders[42]. The role of 5-HT and its receptor subtypes in mediating the symptoms of anxiety, panic and obsessions is complex. Specific attention has been drawn to the 5-HT1A and 5-HT2C receptor subtypes. 5-HT released from the nerve terminal binds to the postsynaptic 5-HT2C receptor subtype, which mediates anxiety[40,48]. 5-HT1A is an auto- receptor on the presynaptic neuron which, when stimulated, inhibits the release of 5-HT from the presynaptic neuron into the synapse[43]. Serotonergic neurons are implicated in the alteration of appetite, energy, sleep, mood and cognitive function in anxiety[48]. Its role in anxiety is supported by its modulating effect on the locus ceruleus and its projections to the amygdale; anatomical structure almost conclusively implicated in anxiety. Fear and stress activate serotonergic pathways[41,49].

Tachykinins and Substance P

Tachykinins throughout the brain, spinal cord, and peripheral nervous system are implicated in the pathophysiology of anxiety. Pre-clinical studies suggest anxiolytic effects of NK1 receptor antagonists[50]. Further, disruption of the NK1 receptor by knockout techniques results in reduced anxiety in response to stress[51].

Corticotropin-releasing Factor

Some abnormalities in the- hypothalamic-pituitary-adrenal axis and central corticotropin-releasing factor (CRF) neuronal functioning have been identified in several anxiety disorders. Patients with combat-related posttraumatic stress disorder have a pattern of central overproduction of CRF, with low plasma cortisol and up-regulation of lymphocyte corticosteroid receptors[41,44]. Corticotropin-releasing factor, a 41 amino acid peptide, is a neurotransmitter

within the central nervous system (CNS) that acts as a key mediator of autonomic, behavioral, immune, and endocrine stress responses. The peptide appears to be anxiogenic, depressogenic, and proinflammatory and leads to increased pain perception. Gama-Aminobutyric acid (GABA) inhibits CRF release[40].

Corticotropin-releasing Hormone

CRH is important mediator of the stress response, as reflected by the stress-induced release of CRH from the hypothalamus into the hypthalamo-pituitary portal circulation resulting in activation of HPA axis and the increased release of cortisol and DHEA[43]. The following brain regions have neurons that contain CRH: the PFC, the cingulate cortex (CeA), the bed nucleus of the stria terminalis (BNST), the nucleus accumbens (NAc), the periaqueductal gray (PAG), and brain stem nuclei, such as the major norepinephrine (NE)–containing nucleus, the locus ceruleus (LC) and the serotonin nuclei in the dorsal and median raphe[44]. Amygdala CRH neuronal hyperactivity may mediate fear related behaviors, while excessive cortical CRH may reduce reward expectation. Early life stress results in chronic elevation of brain CRH activity and the individual response to heightened CRH function may depend upon the social environment, past trauma history, and behavioral dominance[52]. In contrast, preliminary data suggest that stimulation of the CRH-2 receptor results in reduced anxiety-related behaviors. Research into the role of CRH in the pathophysiology of anxiety disorders has been limited by the lack of CRH receptor ligands useful for brain imaging in human subjects. Increased cerebrospinal fluid (CSF) levels of CRH have been linked to PTSD by several studies[52]. Corticotropin-releasing factor mediates endocrine, autonomic, and behavioral responses to stress[53]. Administration of antisense oligodeoxynucleotides corresponding to the start-coding region of CRH mRNA to stressed rats decreased CRH biosynthesis and reduced anxiety-related behavior[54].

Cortisol

Psychological stress has been demonstrated to increase the synthesis and release of cortisol. Cortisol has many different functions including mobilization of energy stores, increased arousal, vigilance, focused attention, and memory formation, inhibition of the growth and reproductive system, and containment of the immune response. The behavioral effects of cortisol are due, in part, to regulatory effects on the hippocampus, amygdala, and prefrontal cortex (PFC)[42].

Cortisol increases the effects of CRH on conditioned fear, and facilitates the encoding of emotion-related memory[43]. Many of the effects of cortisol, particularly those outside the hypothalamo- pituitary-adrenal (HPA) axis, are mediated via an interaction with the glucocorticoid receptor (GR). Another adrenal steroid that is intimately involved in the stress response is dehydroepiandrosterone (DHEA). DHEA is secreted with cortisol in response to fluctuating adrenocorticotropic hormone (ACTH) levels. There is evidence that DHEA possesses antiglucocorticoid and antiglutamatergic properties in the brain. Since peripherally produced DHEA is thought to be a major source of brain DHEA, it is likely that within the brain regionally specific metabolism of DHEA may ultimately control the nature of DHEA's effects on cognition and behaviour[43]. Dysregulations in cortisol secretion and in the hypothalamic pituitary axis, which modulate stress responses, have been observed in anxiety disorders such as GAD and PTSD [52].

Other substances implicated in anxiety include neuropeptide Y, tachykinins and glutamate.

Neuropeptide Y (NPY**)** is among the most abundant neuropeptides in mammalian brain with high concentrations in the LC; paraventricular nucleus of the hypothalamus; septohippocampal neurons; nucleus of soli- tray tract; and ventrolateral medulla[43]. Moderate levels are found in the amygdala, hippocampus, cerebral cortex, basal ganglia, and the thalamus. NPY has been shown to have anxiolytic activity and to impair the consolidation of memories. Tachykinins throughout the brain, spinal cord, and peripheral nervous system are implicated in the pathophysiology of anxiety. Pre-clinical studies suggest anxiolytic effects of NK1 receptor antagonists[51].

HPA Axis and Anxiety

The HPA axis is an interactive system of hormones released in response to stress. The release of CRF by the hypothalamus prompts the pituitary to disperse adrenocorticotropin-releasing hormone (ACTH) into the bloodstream. ACTH is detected by the adrenal cortex, facilitating the release of glucocorticoids such as cortisol[52,43]. Negative feedback occurs when cortisol binds to glucocorticoid receptors on the hypothalamus and pituitary, suppressing the subsequent release of CRF and ACTH[42,43]. High levels of anxiety result in negative physiological manifestations, such as elevated blood cortisol levels and increased blood pressure and heart rate, leading to

slower wound healing, diminished immune response, and increased risk of infection[55]. The stress response in humans involves a cascade of hormonal events, including the release of corticotropin-releasing factor (CRF), which, in turn, stimulates the release of corticotropin, leading to release of the stress hormones (glucocorticoids and epinephrine) from the adrenal cortex[44]. The glucocorticoids typically exert negative feedback to the hypothalamus, thus decreasing the release of CRF[56]. As a result, when humans chronically and erroneously believe that a homeostatic challenge is about to occur, they enter the realm of neurosis, anxiety, and paranoia. The amygdala is the primary modulator of the response to fear- or anxiety-inducing stimuli. It is central to registering the emotional significance of stressful stimuli and creating emotional memories. Thus, the stress response involves activation of the hypothalamic-pituitary-adrenal axis. This axis is hyperactive in depression and in anxiety disorders[55].

Galanin

Galanin suppress the noradrenergic, serotonergic and dopaminergic neurons[57]. Endogenous galanin exert anxiolysis in amygdale in response to stressful conditions [58]. However, exogenous galanin has produced variable effects in anxiety states. Intracerebroventricular administration of galanin reduced anxiety-like behavior, whereas, injection into amygdala produced an anxiogenic effect[59].

Glutamatergic transmission

Glutamate levels are profoundly increased upon exposure to aversive stimuli and stress[60]. Antagonism of endogenous excitatory amino acid neurotransmission in the DLPAG reverse behavioral suppression. Glutamate antagonists show an anxiolytic-like profile in the elevated plus maze[61].

Glucagon like peptide1

Glucagon-like peptide-1 is widely present in brain stem neurons, which innervate locus cerulus, hippocampus and amygdala. Injection of Glucagon-like peptide-1 into amygdala produced anxiogenic effect[62].

Melanin concentrating hormone (MCH)

MCH (1) receptor mediate the regulation of emotion and stress responses. Blockade of MCH (1) receptors results in antidepressant and anxiolytic effects. The effects of MCH (1) receptor antagonists in animal models, together with their rapid onset of effect and lack of adverse CNS effects advocate their investigation as potential treatments for depression and anxiety disorders[63].

Melatonin

Melatonin controls sleep and rhythm, which are generally disturbed in anxiety. Melatonin produce anxiolysis, which is blocked by Flumazenil, a GABAA receptor antagonist[64].

Norepinephrine (NE)

Majority of noradrenergic neurons are found in the locus ceruleus. Altered noradrenergic signaling is linked to anxiety disorders. Sustained stimulation of locus ceruleus results in manifestation of anxiety symptoms. Stress-induced release of NE facilitates a number of anxiety-like behavioral responses too including stress-induced reduction of open-arm exploration on the elevated plus-maze, stress-induced reduction of social interaction behavior[65]. Norepinephrine transporter-deficient mice have increased circulating catecholamines and elevated heart rate and blood pressure[66]. Blockers of adrenergic β receptors have also been utilized clinically for treatment of performance anxiety[67].

Neuropeptide Y

Activation of Y1 and Y5 receptors of NPY in the basolateral amygdala produces dose-dependent anxiolytic-like effects, which is reversed by α2- adrenergic receptor antagonists. Moreover, mutant mice lacking NPY show increased anxiety-related behavior[68].

Neuroactive steroids (Neurosteroids)

These are steroids synthesized from cholesterol in glial cells and neurons have capability to alter neuronal excitability. They exert anxiolysis through GABAA receptors[69]. Deoxycorticosteroid derivatives like 3á, 5á-tetrahydroprogesterone (3á,5á-THP) and

3á,5átetrahydrodeoxycorticosterone (3á,5á-THDOC) bind at GABA-A receptors to enhance GABA-induced chloride currents, similar to benzodiazepines. Neurosteroids may be tested as therapeutic target for the treatment anxiety disorders with improved efficacy without motor and cognitive side effects[70].

Acetylcholine

Two different lines of evidence exist regarding cholinergic modulation of anxiety state. Cholinergic input to hippocampus is enhanced in response to anxiogenic and stressful stimuli, wherein, muscarinic M1 receptors mediate induction of anxiety states through noradrenergic pathways[71]. On the other hand, nicotine facilitate GABAergic neurons and induce anxiolysis and anxiolysis is also being observed after by increasing acetylcholine levels on administration of acetylcholinesterase inhibitor physostigmine in dorsal or the ventral hippocampus[72].

Adenosine

Adenosine is formed by hydrolysis of 5-adenosine monophosphate and is transformed to inosine, which is then stored as adenosine triphosphate. Adenosine through A1 and A2A receptors exert anxiolysis through its facilitatory influence on GABA release in the septum and hippocampus[73,74].

Arginine vasopressin (AVP)

This nonapeptide regulates Hypothalamus-pituitary adrenal system by enhancing the effects of CRH on adrenocorticotropic hormone (ACTH) release. AVP exert its effects through G protein-coupled receptors *viz.* V1A and V1B. SSR149415, selective and orally active non-peptide antagonist of vasopressin V (1B) receptors produced anxiolytic-like activity[75].

Atrial natriuretic peptide (ANP*)*

Atrial natriuretic factor is produced by heart and released into the circulation. Intracerebroventricular (i.c.v.) administration of ANP elicit anxiolytic activity in the open field, the social interaction, and the elevated plus maze tests[76]. Central and peripheral administration of atriopeptin II, an amino acid residue peptide of ANP also produce anxiolysis in elevated plus maze test[77].

Cannabinoids

They suppress flow of glutamate, norepinephrine and dopamine in hippocampus and cortex and interfere with GABAergic transmission in the amygdale and hippocampus and frontal cortex[78]. Due to complex pattern of influence of cannabinoids on release of neurotransmitters, both anxiolytic as well as anxiogenic profile has been observed[79].

Cholecystokinin (CCK)

CCK is one of the most abundant brain neuropeptides. CCK-immunoreactive fibers and CCK (2) receptors are rich in anatomical locations like periaqueductal gray (PAG), which mediate anxiety. Neuronal expression of CCK-2 receptor result in manifestation of anxiety-like behaviors, attenuated by diazepam[80].

Glutamatergic transmission

Glutamate levels are profoundly increased upon exposure to aversive stimuli and stress[60]. Antagonism of endogenous excitatory amino acid neurotransmission in the DLPAG reverse behavioral suppression. Glutamate antagonists show an anxiolytic-like profile in the elevated plus maze[61].

Glucagon like peptide1

Glucagon-like peptide-1 is widely present in brain stem neurons, which innervate locus cerulus, hippocampus and amygdala. Injection of Glucagon-like peptide-1 into amygdala produced anxiogenic effect[62].

TREATMENT OF ANXIETY DISORDERS

In general, anxiety disorders are treated with medication, specific types of psychotherapy, or both. Treatment choices depend on the problem and the person's preference. Before treatment begins, a doctor must conduct a careful diagnostic evaluation to determine whether a person's symptoms are caused by an anxiety disorder or a physical problem. If an anxiety disorder is diagnosed, the type of disorder or the combination of disorders that are present must be identified, as well as any coexisting conditions, such as depression or substance abuse.

Sometimes alcoholism, depression, or other coexisting conditions have such a strong effect on the individual that treating the anxiety disorder must wait until the coexisting conditions are brought under control. People with anxiety disorders who have already received treatment should tell their current doctor about that treatment in detail. If they receive medication, they should tell their doctor what medication was used, what the dosage was at the beginning of treatment, whether the dosage was increased or decreased while they were under treatment, what side effects occurred, and whether the treatment helped them become less anxious. If they receive psychotherapy, they should describe the type of therapy, how often they attended sessions, and whether the therapy was useful. Often people believe that they have "failed" at treatment or that the treatment didn't work for them when, in fact, it was not given for an adequate length of time or was administered incorrectly. Sometimes people must try several different treatments or combinations of treatment before they find the one that works for them[37,2].

Medication will not cure anxiety disorders, but it can keep them under control while the person receives psychotherapy. Medication must be prescribed by physicians, usually psychiatrists, who can either offer psychotherapy themselves or work as a team with psychologists, social workers, or counselors who provide psychotherapy. The principal medications used for anxiety disorders are antidepressants, anti-anxiety drugs, and beta-blockers to control some of the physical symptoms. With proper treatment, many people with anxiety disorders can lead normal, fulfilling lives[37].

Antidepressants

Antidepressants were developed to treat depression but are also effective for anxiety disorders. Although these medications begin to alter brain chemistry after the very first dose, their full effect requires a series of changes to occur; it is usually about 4 to 6 weeks before symptoms start to fade. It is important to continue taking these medications long enough to let them work[37].

SSRIs

Some of the newest antidepressants are called selective serotonin reuptake inhibitors, or SSRIs. SSRIs alter the levels of the neurotransmitter serotonin in the brain, which, like other

neurotransmitters, helps brain cells communicate with one another. Fluoxetine (Prozac®), sertraline (Zoloft®), escitalopram (Lexapro®), paroxetine (Paxil®), and citalopram (Celexa®) are some of the SSRIs commonly prescribed for panic disorder, OCD, PTSD, and social phobia. SSRIs are also used to treat panic disorder when it occurs in combination with OCD, social phobia, or depression. Venlafaxine (Effexor®), a drug closely related to the SSRIs, is used to treat GAD. These medications are started at low doses and gradually increased until they have a beneficial effect. SSRIs have fewer side effects than older antidepressants, but they sometimes produce slight nausea or jitters when people first start to take them. These symptoms fade with time. Some people also experience sexual dysfunction with SSRIs, which may be helped by adjusting the dosage or switching to another SSRI[37].

Tricyclics

Tricyclics are older than SSRIs and work as well as SSRIs for anxiety disorders other than OCD. They are also started at low doses that are gradually increased. They sometimes cause dizziness, drowsiness, dry mouth, and weight gain, which can usually be corrected by changing the dosage or switching to another tricyclic medication. Tricyclics include imipramine (Tofranil®), which is prescribed for panic disorder and GAD, and clomipramine (Anafranil®), which is the only tricyclic antidepressant useful for treating OCD[37].

MAOIs

Monoamine oxidase inhibitors (MAOIs) are the oldest class of antidepressant medications. The MAOIs most commonly prescribed for anxiety disorders are phenelzine (Nardil®), followed by tranylcypromine (Parnate®), and isocarboxazid (Marplan®), which are useful in treating panic disorder and social phobia. People who take MAOIs cannot eat a variety of foods and beverages (including cheese and red wine) that contain tyramine or take certain medications, including some types of birth control pills, pain relievers (such as Advil®, Motrin®, or Tylenol®), cold and allergy medications, and herbal supplements; these substances can interact with MAOIs to cause dangerous increases in blood pressure. The development of a new MAOI skin patch may help lessen these risks. MAOIs can also react with SSRIs to produce a serious condition called "serotonin syndrome," which can cause confusion, hallucinations, increased sweating, muscle

stiffness, seizures, changes in blood pressure or heart rhythm, and other potentially life-threatening conditions[37].

Anti-Anxiety Drugs

High-potency benzodiazepines combat anxiety and have few side effects other than drowsiness. Because people can get used to them and may need higher and higher doses to get the same effect, benzodiazepines are generally prescribed for short periods of time, especially for people who have abused drugs or alcohol and who become dependent on medication easily. One exception to this rule is people with panic disorder, who can take benzodiazepines for up to a year without harm. Clonazepam (Klonopin®) is used for social phobia and GAD, lorazepam (Ativan®) is helpful for panic disorder, and alprazolam (Xanax®) is useful for both panic disorder and GAD. Some people experience withdrawal symptoms if they stop taking benzodiazepines abruptly instead of tapering off, and anxiety can return once the medication is stopped. These potential problems have led some physicians to shy away from using these drugs or to use them in inadequate doses. Buspirone (Buspar®), an azapirone, is a newer anti-anxiety medication used to treat GAD. Possible side effects include dizziness, headaches, and nausea. Unlike benzodiazepines, buspirone must be taken consistently for at least 2 weeks to achieve an anti-anxiety effect[37].

Beta-Blockers

Many symptoms of anxiety(palpitation, rise in BP, shaking, tremor, GI hurrying, etc.) are due to sympathetic over activity, and these symptoms reinforce anxiety. Propranolol and other non selective beta blockers help anxious patients troubled by these symptoms, by cutting the vicious cycle and provide symptomatic relief. They do not affect psychological symptoms such as worry, tension and fear, but are valuable in acutely stressful situations. They may be used for performance /situational anxiety or adjuvant to BZDs. The role of beta blockers in anxiety disorders is quite limited[85]. Beta-blockers, such as propranolol (Inderal®), which is used to treat heart conditions, can prevent the physical symptoms that accompany certain anxiety disorders, particularly social phobia. When a feared situation can be predicted (such as giving a speech), a doctor may prescribe a beta-blocker to keep physical symptoms of anxiety under control[37].

Table 4. Major Classes Of Medications Used For Various Anxiety Disorders[14,15]

Class	Generic name	Used for	M.O.A.	Advantages	Limitations
Anticonvulsants	Gabapentin	SAD	Affect GABA	Usually effective within 2-4 Weeks	Sedation
Azaspirones	Buspiron	GAD	Enhances the activity of serotonin	Less sedating than benzodiaze-pines	Works slowly
Benzodiazepines	Lorazepam Clonazepam Oxazepam Diazepam Alprazolam	GAD, SAD, Panic Disorder	Enhance the function of GABA	Fast-acting, some people feel better the first day	Potentially habit-forming, can cause drowsiness, can produce withdrawal symptoms, discontinuation should be done slowly
Beta blockers	Propanolol Atenolol	SAD	Reduce ability to produce adrenaline	Fast acting; n ot habit forming	Should not be used with pre-existing medical conditions, such as asthma, congestive heart failure, diabetes, vascular disease, hypothyroidism and angina pectoris
Monoamine oxidase inhibitors (MAOIs)	Selegilene Isocarboxid Phenelzine Tranylcypromine	Panic disorder, SAD, PTSD	Block the effect of an important brain enzyme, preventing the breakdown of serotonin and noradrenaline	Effective for many people, especially for patients not responding to other medications, 2-6 weeks until improvement occurs	Strict dietary restrictions and potential drug interactions, changes in blood pressure, moderate weight gain, reduced sexual response, insomnia
Selective	Citalopram	Panic	Affect the	Effective, with	Some people experience
serotonin reuptake inhibitors (SSRIs)	Fluvoxamine Paroxetine Fluoxetine Sertraline	disorder, OCD, SAD, GAD	concentration of serotonin	fewer side effects than other medications. 4-6 weeks until improvement occurs	nausea, nervousness and diminished sex drive
Tricyclic antidepressants (TCAs)	Nortriptyline Amitriptyline Imipramine	Panic disorder, PTSD, OCD	Regulates serotonin and/or noradrenaline in the brain	Effective for many people, may take 2-6 weeks until improvement occurs	Dry mouth, constipation, blurry vision, difficulty urinating, dizziness, low blood pressure, moderate weight gain, sexual side effects

1. **Note:** GAD = Generalized anxiety disorder, OCD = Obsessive compulsive disorder, PTSD = Post Traumatic stress disorder, SAD=Social anxiety disorder.

MANAGEMENT OF ANXIETY

Anxiety disorders are the most prevalent of psychiatric disorders, however less than 30% of individuals who suffer from anxiety disorders seek treatment[3]. People with anxiety disorders can benefit from a variety of treatments and services. Following an accurate diagnosis, possible treatments include [86,37] psychological treatments and mediation.

PSYCHOLOGICAL TREATMENTS

Psychotherapy is almost always the *treatment of choice* except in cases where anxiety is so severe that immediate relief is necessary to restore functioning and to prevent immediate and severe consequences. This includes the following:

- ***Behavioral therapies:*** These focus on using techniques such as guided imagery, relaxation training, biofeedback (to control stress and muscle tension); progressive desensitization, flooding as means to reduce anxiety responses or eliminate specific phobias. The person is gradually exposed to the object or situation that is feared. At first, the exposure may be only through pictures or audiotapes. Later, if possible, the person actually confronts the feared object or situation. Often the therapist will accompany him or her to provide support and guidance.
- ***Cognitive-behavioral therapy (CBT):*** Cognitive-behavioral therapy (CBT) is very useful in treating anxiety disorders. The cognitive part helps people change the thinking patterns that support their fears, and the behavioral part helps people change the way they react to anxiety-provoking situations. In this therapy, people learn to deal with fears by modifying the ways they think and behave. A major aim of CBT and behavioral therapy is to reduce anxiety by eliminating beliefs or behaviors that help to maintain the anxiety disorder. Research has shown that CBT is effective for several anxiety disorders, particularly panic disorder and social phobia[37]. It has *two* components. The *cognitive component* helps people change thinking patterns that keep them from overcoming their fears. The *behavioral component* of CBT seeks to change people's reactions to anxiety-provoking situations. A key element of this component is exposure, in which people confront the things they fear, i.e., CBT addresses underlying

"automatic" thoughts and feelings that result from fear, as well as specific techniques to reduce or replace maladaptive behavior patterns [37].

- ***Psychotherapy:*** Psychotherapy centers on resolution of conflicts and stresses, as well as the developmental aspects of anxiety disorders solely through talk therapy. Psychotherapy involves talking with a trained mental health professional, such as a psychiatrist, psychologist, social worker, or counselor to learn how to deal with problems like anxiety disorders[81].
- **Psychodynamic therapy:** This therapy**,** first suggested by Freud, is based on the premise that primary sources of abnormal behavior are unresolved past conflicts and the possibility that unacceptable unconscious impulses will enter consciousness.
- **Family therapy and parent training:** Here the focus is on the family and its dynamics. This is based on the assumption that the individuals of a family cannot improve without understanding the conflicts that are to be found in the interactions of the family members. Thus, each member is expected to contribute to the resolution of the problem being addressed[6,42].

HOW LONG DOES PSYCHOLOGICAL TREATMENT TAKE?

The large majority of people who suffer from anxiety disorder are able to reduce or eliminate their anxiety symptoms and return to normal functioning after several months of appropriate psychotherapy. Indeed, many people notice improvement in symptoms and functioning within a few treatment sessions. The patient should be comfortable from the outset with the psychotherapist. Together the patient and psychotherapist should develop an appropriate treatment plan. The patient's cooperation is crucial, and there must be a strong sense that the patient and therapist are collaborating well as a team to treat the anxiety disorder. No one plan works well for all the patients. Treatment needs to be tailored to the needs of the patient depending on the type of disorder from which the individual suffers. The psychotherapist and patient should work together to assess whether a treatment plan seems to be on track. Patients respond differently to treatment, and adjustments to the plan sometimes are necessary[37].

CONCLUSION

Anxiety disorders, in addition to being prevalent, are associated with vital functional impairments. Even though there have been recent advances in the management and understanding of these disorders, the treatment of anxiety remains a challenge for the clinical

practice. Several interventions have proven to be efficient to reduce anxiety symptoms; however, many patients remain symptomatic and disabled. Anxiety disorders are among the most common mental disorders, and they create a substantial burden for patients and their families. Anxiety disorders are often chronic and associated with significant functional impairment and reduced quality of life. A systematic approach of treatment should include patient education, examination of potential comorbidities empirically proven psychological and pharmacologic treatments with adequate monitoring and duration.

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